Controlled Transdermal Delivery of Fentanyl: Characterizations of Pressure-Sensitive Adhesives for Matrix Patch Design[*]

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Abstract □ Transdermal delivery of fentanyl from various adhesive matrix formulations to achieve a steady-state skin flux was investigated. For this purpose, various pressure-sensitive adhesives selected from the three chemical classes of polymers (polyisobutylene (PIB), acrylate, and silicone adhesives) were characterized with respect to fentanyl's solubility, diffusion coefficient, and permeability coefficient. The solubility of fentanyl in various pressure-sensitive adhesives at 32 °C was determined by the drug absorption–desorption method. The solubilities of fentanyl in these adhesives were in the following order: acrylate > silicones > PIB. The permeability coefficient and diffusion coefficient of fentanyl in these adhesives were determined by the membrane diffusion method. The diffusion coefficient rank order was silicone-2920 > silicone-2675 ≥ acrylate > PIB. The release profiles of fentanyl in the aqueous buffer from these adhesives with 2–4% drug loading was evaluated. The release rate of fentanyl from the acrylate polymer was significantly higher than those of silicone and PIB adhesives. The in vitro flux of fentanyl through cadaver skin from various adhesives with 2% drug loading was determined at 32 °C using modified Franz diffusion cells. The skin fluxes of fentanyl from silicone-2920 and PIB adhesives were 6.3 ± 0.7 and 3.1 ± 0.3 $\mu g/cm^2/h$, respectively. On the other hand, the skin fluxes of fentanyl from acrylate and silicone-2675 adhesive matrices were about 1 $\mu g/cm^2/h$. The effect of drug loading on skin flux was investigated using PIB as a model adhesive. The drug released in the phosphate buffer (pH = 6.0) increased linearly as the drug loading in the PIB was increased from 1% to 4%; and as the drug loading exceeded 4%, an initial burst effect followed by a zero-order release was observed. The skin flux of fentanyl increased proportionally as the drug loading in the PIB adhesive was increased from 1 to 4%, and a plateau was reached beyond 4% drug loading. These results suggest that fentanyl concentration in the PIB adhesive might have reached saturation above 4% drug loading and that the optimum skin flux was accomplished from such a system because of attainment of maximum thermodynamic activity.

Introduction

Fentanyl, a potent narcotic analgesic, is used clinically for the relief of acute postoperative and chronic cancer pain.[1] Because of a short half-life and a high metabolic clearance in humans, repeated IV bolus doses or continuous IV infusion is required to sustain analgesic plasma levels. Alternatively, fentanyl might be delivered transdermally to sustain analgesia for longer periods. Transdermal delivery of fentanyl offers several advantages over the conventional dosage forms.[2] The skin permeability of fentanyl through human cadaver skin was reported.[3,4] We have previously demonstrated that fentanyl was relatively more skin permeable than the other narcotic analgesic analogs because of its suitable physicochemical properties for skin transport. Therefore, fentanyl is a good candidate for transdermal delivery. The minimum effective plasma concentration for fentanyl to induce analgesia was reported to be 1–2 ng/mL.[5] Because the total systemic clearance of fentanyl in humans is 50 L/h, an input rate of 50–100 $\mu g/h$ is adequate to induce analgesia in humans.[6] Such a delivery rate is readily achievable, and the drug action can be sustained for an extended period by designing a suitable transdermal device.[7,8]

In recent years, various pressure-sensitive adhesives were considered for fabricating transdermal delivery systems. To fabricate such a transdermal device, the drug was either dissolved or dispersed in a polymeric solution, and a thin film of desired thickness was then prepared by the solvent-cast method.[9] The rate of release of drug from such an adhesive matrix is governed by drug solubility and diffusion coefficients in polymer. Usually, these parameters were greatly influenced by the physicochemical properties of the polymer or adhesive. Therefore, it is important to evaluate the physicochemical parameters of an adhesive to design a suitable transdermal system that would eventually deliver a drug at a desired rate through skin for an extended period. In the present investigation, polyisobutylene (PIB), silicones, and acrylate pressure-sensitive adhesives were considered for characterizations of matrix formulations with respect to fentanyl's solubility, membrane partition coefficient, and diffusion coefficient. The in vitro skin flux of fentanyl through human cadaver skin from matrix formulations was investigated. In addition, the relationship between the fentanyl release rate from an adhesive matrix into aqueous media and skin flux was evaluated.

Experimental Section

Materials—Fentanyl base was purchased from Mallinckrodt (Paris, CT). [redacted] polymers (ethyl acetate and toluene) was obtained from Monsanto (St. Louis, MO). Two types of silicone pressure-sensitive adhesives (silicone-2920 and silicone-2675) in n-Frean solution (solid content varied from 35% to 50%) and silicone oil (viscosity: 100 cSt) were a gift sample from Dow Corning (Midland, MI). PIB (Vistanex LM-MS, average molecular weight 44 000, and Vistanex MH L-100, average molecular weight 1 450 000) and Indopol (resin) in a solid state were purchased from Exxon Chemical Co. (Houston, TX). The polyester film (Release Liner) was obtained from 3M Co. (St. Paul, MN). All other chemicals used in the study were of analytical reagent grade and used as such without any further purification.

Preparation of Adhesive Matrices—Acrylate and silicone adhesives were used as received, but the PIB solution in hexane was prepared in the laboratory. [redacted] Indopol (resin) was added to the solution and mixed using a rotary type mixer for several hours at room temperature until all the PIB was dissolved in hexane. The solid content of each polymeric solution was determined by driving off the organic solvents from the known weight of the solution.

A known quantity of fentanyl base was added to each polymeric solution. The drug was completely dissolved at low loading or

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Exhibit A

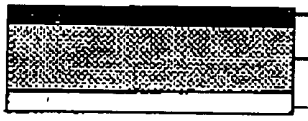

Figure 1—Schematic representation of monolithic matrix transdermal device.

dispersed uniformly at high loading in the adhesive solution using a rotary mixer (occasionally a vortex mixer) for more than 2 h at room temperature. The solutions were allowed to set in the containers for visual checking of whether the drug was dissolved or uniformly dispersed. The solutions were then cast on an untreated (sticky) surface of polyester film using a Gardener knife setup. The films were allowed to set at room temperature for 10 min and were subsequently oven-dried at 50 °C for about 15–30 min to remove the residual organic solvents. The films were covered with another polyester liner in such a fashion that silicone-treated (nonsticky) surface was in contact with adhesive film, enabling easy removal of release liner for later use (Figure 1). The film thicknesses of monolithic slabs were measured by difference using a microcaliper.

Drug Release—The monolithic slabs of known areas were attached to glass slides using two-sided 3M adhesive tapes. The whole slides were then immersed separately in a 50-mL-capacity, amber-colored bottle containing 25 mL of sodium phosphate buffer (pH = 6). The buffer medium was stirred at room temperature throughout the experiment using a Teflon-coated small magnetic bar. The glass slides were positioned so that the upper surface of the polymer was completely exposed to the buffer solution and so that the stir bars would not stick to the films and impede the drug release from the system. At specified times, 1-mL samples were withdrawn from the bottles and assayed by an HPLC–UV method.

Partition Coefficient Determination—The partition coefficient of fentanyl between the adhesive membrane and water was determined by the absorption–desorption method. Several adhesive films without any drug were prepared by the film casting method as described. The thicknesses of the films were determined by a microcaliper. These polymeric slabs of known dimensions were immersed in the saturated free base solution in pure water at 32 °C for at least 2 weeks to reach equilibrium. The drug concentration in the aqueous solution was monitored until no more drug was depleted from the media. Each slab was then removed from the solution, and the exposed surface was gently wiped with soft tissue paper to dry the adhesive film. The dried film was transferred to an amber-glass bottle, and 50 mL of fresh phosphate buffer (pH = 6) was added to release the absorbed drug from the adhesive. The solution was stirred overnight to facilitate the release of the drug into the buffer medium. A 1-mL sample was withdrawn and assayed by HPLC. Subsequent samples were withdrawn to assure a complete release of the drug from matrix into an aqueous buffer medium. The solubility of fentanyl in each polymer was determined from the total amount of drug released into the buffer divided by the volume of the slab. The partition coefficient of fentanyl (K_p) in the polymers was determined from the equation

$$K_p = C_p/C_s \tag{1}$$

where C_p is the concentration of fentanyl in the polymer and C_s is the drug solubility in pure water. The solubility of fentanyl in pure water was determined to be 0.122 mg/mL at 32 °C.

Membrane Permeation—The films of various pressure-sensitive adhesives were prepared by the film casting method as described above, using siliconized polyester film. Each dried film was sandwiched between two nonwoven fibers (Cerex, James River Co., NJ). The nonwoven fiber provided a good mechanical support to the thin polymeric films and offered very little or no diffusional resistance for drug transport. Moreover, sandwiching these adhesives between the two nonwoven fibers precluded the sticking tendency of the adhesives to glass diffusion cells.

Circular slabs of polymeric films were punched and mounted between side-by-side diffusion cells. The receiver compartment was filled with 7.5 mL of phosphate buffer (pH = 6.0), and the donor compartment was charged with a saturated fentanyl free base solution in pure water (pH 8.8–9). The diffusion cells were carefully placed on a multiple stirring plate for continuous mixing of receiver fluid throughout the experiment. The stirring plate was placed in an oven maintained at 32 °C. At predetermined times, 1-mL samples were withdrawn from the receiver compartment and replaced with an equal volume of previously warmed phosphate buffer. The samples were assayed by an HPLC–UV method.

Table 1—Solubility and Partition Coefficient of Fentanyl in Various Pressure-Sensitive Adhesives at 32 °C

Adhesive	Solubility (C_p) (mg/mL)	K_{pw}[a]
[redacted]		6.5
		179.0
		164.0
		15.6

[a] $K_{pw} = C_p/C_s$; solubility in pure water (C_s) = 0.122 mg/mL.

Skin Permeation—Human cadaver skin was used for the permeation studies. Samples of skin were removed from the abdomen or thigh of human cadavers within 48 h postmortem using a dermatome set at 300 μm. Epidermal layers were separated from the split-thickness skin by immersing each skin section in water at 60 °C for 30 s. The epidermis was teased from the dermis using forceps. The separated epidermal layer was used as such for the skin permeation studies or wrapped in a Saran film and stored at −20 °C for later studies. The epidermal layers were cut into small circular patches and checked immediately for any leaks before application of the transdermal system. Transdermal patches measuring approximately 1.3 cm^2 were die cut and applied with slight pressure to the dorsal side (stratum corneum) of the epidermal membrane. Each membrane was carefully mounted on a Franz diffusion cell of approximately 7.5-mL receiver capacity and fastened with a rigid clamp. The receiver compartments were filled with isotonic buffer (pH = 6) and were stirred throughout the diffusion experiment. The cells were placed in a 32 °C temperature-controlled oven. At predetermined times, 1-mL samples were withdrawn from the receiver compartment and replaced with previously warmed phosphate buffer.

Drug Assay—Fentanyl was assayed by HPLC with UV detection at 225 nm. A μBondapak C_{18} column and acetonitrile/buffer (60:40, pH 6.0) as a mobile phase were used. The flow rate was 1.0 mL/min. Calibration curves were obtained by plotting the peak area of the authentic drug as a function of drug concentration.

Data Analysis—The steady-state flux (J_s) of fentanyl through the adhesive film was determined from the following equations:

$$(dM/dt)/A = J_s = P_m \Delta C_1 = P_m C_s \tag{2}$$

and

$$D_{p(lag)} = L^2/6T_{lag} \tag{3}$$

$$D_{p(ss)} = P_m L/K_{p/w} \tag{4}$$

where dM/dt is the cumulative amount of drug permeated per unit time, A is the effective diffusion area, $D_{p(lag)}$ is the diffusion coefficient estimated by lag time, $D_{p(ss)}$ is the steady-state diffusion coefficient, C_s is the drug concentration (solubility) in donor assuming less than 10% drug depleted from the donor compartment, L is the membrane thickness, and T_{lag} is the lag time. A perfect sink condition was maintained throughout the membrane diffusion experiments.

The skin flux was determined from Fick's law of diffusion as follows:

$$J_s = (V\,dC/dt)/A \tag{5}$$

where J_s is the skin flux (mg/cm²·h), C is the cumulative drug concentration in the receiver fluid at time t, V is the receiver volume (mL), and A is the active diffusion area (cm²).

Results and Discussion

Solubility and Permeability of Fentanyl in Adhesive Films—The solubilities and polymer/water partition coefficients (K_{pw}) of fentanyl as determined by the drug-uptake method are summarized in Table 1. It is important to note that silicone-2920 and PIB adhesives are pure moderately

Table 2—Permeation of Fentanyl through Various Pressure-Sensitive Adhesives at 32 °C[a]

Adhesive	L (μm)	J_s (μg/cm²/h)	T_{lag} (h)	P_m (cm/h)	$D_{p(lag)}$ (cm²/s)	$D_{p(ss)}$ (cm²/s)	$D_{p(ss)}/D_{p(lag)}$
Acrylate	70	16.9	4.5	1.4×10^{-7}	5.1×10^{-10}	1.5×10^{-9}	2.9
Silicone-2675	104	9.9	7.7	8.1×10^{-7}	6.5×10^{-10}	1.4×10^{-9}	2.1
Silicone-2920	61	12.6	0.45	1.0×10^{-7}	3.9×10^{-9}	1.1×10^{-8}	2.9
PIB	71	0.23	21.2	1.9×10^{-9}	1.1×10^{-10}	5.7×10^{-10}	5.2

[a] $D_{p(ss)} = P_m L / K_{p/w}$; the $K_{p/w}$ values are taken from Table 1. Each value is the mean of two or three independent membrane diffusion experiments which did not vary from each other more than 10%.

hydrophobic than silicone-2675 and acrylate adhesives. The solubilities of fentanyl in silicone-2675 and acrylate adhesives were considerably higher than those in silicone-2920 and PIB. This implied that fentanyl was relatively more soluble in moderately hydrophobic adhesives. The $K_{p/w}$ of fentanyl in the PIB and silicone-2920 adhesives was the lowest among the other adhesives studied because of low drug solubility in the former two adhesives. The solubility and partition coefficient of fentanyl in these adhesive membranes were in following rank order: acrylate ≥ silicone-2675 > silicone-2920 > PIB.

Table 2 summarizes various diffusion parameters of fentanyl in the four pressure-sensitive adhesives. In all cases, a saturated aqueous fentanyl free base solution was applied to the donor compartment to maintain the permeant's unit thermodynamic activity throughout the diffusion experiments and a steady-state flux was maintained for at least 28 h. It is interesting that the permeation of fentanyl through the acrylate and silicone adhesive membranes was significantly higher than that of the PIB adhesive. This may be caused in part by the fentanyl's higher solubility and partition coefficient in acrylate and silicone adhesives. The diffusion coefficients ($D_{p(lag)}$) of fentanyl in the adhesive membranes were determined from the knowledge of lag times and membrane thicknesses (eq 3). The diffusion coefficients of fentanyl in these adhesive membranes ranged from 1.0×10^{-9} to 1.1×10^{-10} cm²/s. The diffusion coefficient of fentanyl in silicone-2920 was the highest among the other adhesive membranes, while the diffusion coefficients in silicone-2675 and acrylate adhesives were very similar. On the other hand, the diffusivity of fentanyl in the PIB adhesive was roughly an order of magnitude lower than in the other adhesive membranes.

Alternatively, the steady-state diffusion coefficient ($D_{p(ss)}$) of fentanyl in these adhesives may be determined from the knowledge of P_m, $K_{p/w}$ (Table 1), and membrane thickness (eq 4).[10] The $D_{p(ss)}/D_{p(lag)}$ ratio is presented in the extreme right-hand column of Table 2. The $D_{p(ss)}$ values of fentanyl in acrylate, silicone-2675, and silicone-2920 were roughly 2–3 times higher than the $D_{p(lag)}$ values. In the case of PIB adhesive, however, $D_{p(ss)}$ was about 5 times higher than $D_{p(lag)}$. These data suggest that the $D_{p(lag)}$ value estimated from the T_{lag} method (eq 3) was underestimated because of possible adsorption of fentanyl free base by the adhesive membrane leading to a long lag time to reach a steady state. The adsorption phenomenon was most likely due to relatively high hydrophobicity of fentanyl free base.[11] Therefore, the $D_{p(ss)}$ values determined from independent parameters are more accurate and more reliable than that of $D_{p(lag)}$ as estimated from the extrapolated T_{lag} method. Although the two methods yielded different diffusion coefficient values, the diffusion rank order was essentially the same: silicone-2920 > silicone 2675 ≥ acrylate > PIB.

Release of Fentanyl from Pressure-Sensitive Adhesives—The release profiles of fentanyl into the aqueous medium under perfect sink conditions from various adhesive membranes with 2% drug loading are shown in Figure 2. The

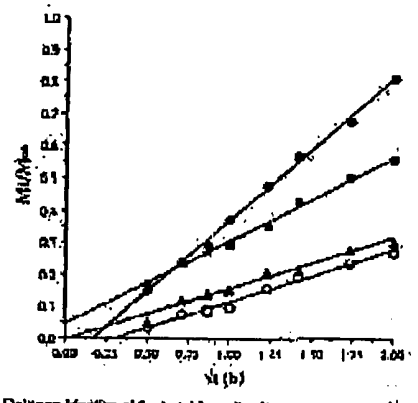

Figure 2—Release kinetics of fentanyl from the four pressure-sensitive adhesives with 2% drug loading into aqueous buffer sink at 32 °C: PIB (○), silicone-2675 (▲), silicone 2920 (■), acrylate (●).

Table 3—Release Rates and Diffusion Coefficients of Fentanyl in Various Pressure-Sensitive Adhesives

Adhesive Type	% w/w Adhesive	% w/w Fentanyl Base	k (min$^{-1/2}$)	D_p (cm²/s)
[redacted]				2.2×10^{-9}
[redacted]				2.8×10^{-9}
Silicone-2675	98	2	1.3	4.6×10^{-9}
Silicone-2675	96	4	1.7	9.4×10^{-9}
Silicone-2920	98	2	2.1	7.6×10^{-8}
PIB	98	2	1.3	2.3×10^{-9}

fraction released (M_t/M_∞) into water from each monolithic matrix device can be predicted from the early-time approximation of Higuchi's equation (when $C_0 < C_s$) as follows:[12]

$$\frac{M_t}{M_\infty} = \sqrt{\frac{AD_p t}{L^2 \pi}} = k\sqrt{t} \qquad (6)$$

where M_t is the amount of drug released at time t, M_∞ is the drug loading in the matrix, D_p is the apparent diffusion coefficient of fentanyl in the adhesive membrane, L is the membrane thickness, C_0 and C_s are the drug loading and drug solubility in the polymer, and k is the release rate constant expressed as min$^{-1/2}$. This relationship applies for all values of $M_t/M_\infty < 0.6$. In all cases, the release kinetics followed the square root of time relationship.

Table 3 summarizes the release rate constant (k) and apparent diffusion coefficient (D_p) of fentanyl from four adhesive matrices with varying amounts of drug loading. An interesting trend in the drug release rate was observed. The release rate of fentanyl from the acrylate adhesive was about 2–3 times higher than the other adhesive membranes studied. In contrast, the drug release rate from the PIB and silicone-2675 matrix at 2% drug loading was the lowest among the other adhesive membranes, while an intermediate release rate from the silicone-2920 adhesive was observed. The increase in fentanyl loading from 2 to 4% in the acrylate and silicone-2675 adhesive matrices had very little effect or no effect on release rate constant and apparent diffusion coefficients of fentanyl. For silicone-2920, however, the effect of drug loading on the release rate kinetics could not be determined because drug loading > 2% resulted in fentanyl crystal formation in the adhesive matrix. The apparent D_p values were slightly higher than those of $D_{p(ss)}$, though the rank order was

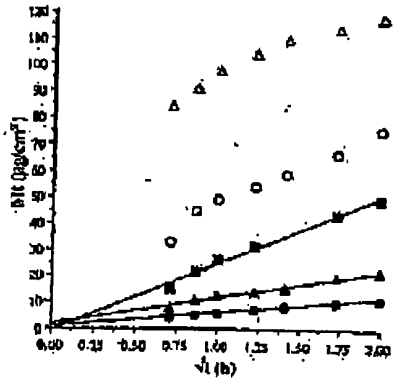

Figure 3—Effect of drug loading in the PIB adhesives on the release profiles of fentanyl into an aqueous buffer sink at 32 °C: 1% (●), 2% (▲), 4% (■), 6% (○), 8% (△). The initial burst effect was observed for those adhesive matrices with drug loading above 4%.

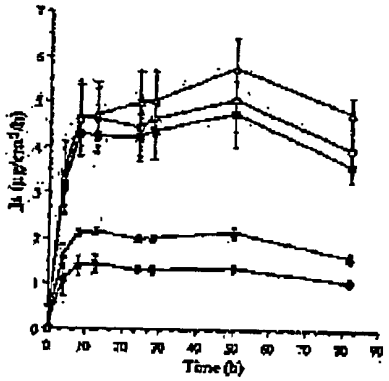

Figure 5—Effect of drug loading on the skin flux of fentanyl from PIB adhesive matrix at 32 °C: 1% (●), 2% (▲), 4% (■), 6% (○), 8% (△). Each value is the mean ± SD of three diffusion experiments.

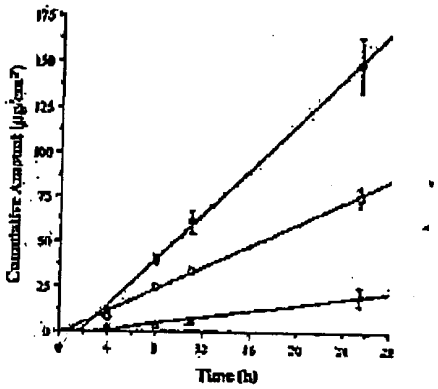

Figure 4—Raw data for the permeation of fentanyl through cadaver skin from the three adhesive matrices with 2% drug loading: acrylate (△), PIB (○), silicone-2920 (●). The silicone-2920 adhesive matrix provided the highest skin flux among the three pressure-sensitive adhesives. Each value is the mean ± SD of three diffusion experiments.

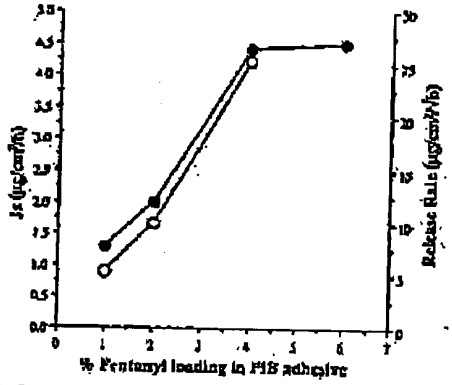

Figure 6—Double plot showing a relationship between skin flux and release rate of fentanyl as a function of drug loading in the PIB adhesive matrix: release rate (○), skin flux (●).

essentially the same for these adhesives. The influence of drug loading in PIB adhesive on release kinetics of fentanyl in water was further investigated and is discussed below.

Figure 3 shows the cumulative amount of fentanyl (M_t) released into water from the PIB adhesives with varying drug loading. The release kinetics followed the square root of time when the drug loading in the PIB adhesive ranged from 1% to 4%. [redacted] The initial burst effect was caused by an instantaneous drug release from the matrix into the aqueous medium. [redacted] The diffusion coefficient of fentanyl in the PIB adhesive (1–4% drug loading) was determined from eq 6. The diffusion coefficients were 2.7×10^{-9}, 2.3×10^{-8}, and 2.9×10^{-9} cm²/s, for 1%, 2%, and 4% drug loading, respectively. These data clearly suggest that the diffusion coefficient of fentanyl in PIB was unaffected by drug loading ranging from 1–4%. The diffusion coefficient of fentanyl at and above 6% loading could not be determined because of the obvious presence of drug crystals in the adhesive matrix leading to an initial burst effect (see Figure 3).

Table 4—Steady-State Flux of Fentanyl through Cadaver Skin from Various Adhesive Matrices with 2% (w/w) Drug Loading at 32 °C

Matrix Formulation	J_s (μg/cm²/h)	T_{lag} (h)
PIB	3.1 ± 0.3	0.5 ± 0.5
Acrylate	0.9 ± 0.2	2.3 ± 0.6
Silicone-2675	1.1 ± 0.2	<1.0
Silicone-2920	4.3 ± 0.7	1.8 ± 0.3
Silicone-2920 + 2% silicone oil	5.3 ± 0.2	1.6 ± 0.5

[a] Each value is the mean ± SD of 3 diffusion experiments.

Skin Permeation of Fentanyl—Figure 4 shows the representative cumulative amount of fentanyl permeated through cadaver skin as a function of time from various matrix patches with 2% drug loading. In all cases, a steady-state skin flux was attained within 4 h after application of the patch and was maintained for at least 24 h. The lag time was determined by extrapolating the linear portion of the cumulative amount of drug permeated versus time plot to the abscissa.

Table 4 compares skin flux and lag time of fentanyl from various matrix formulations with 2% drug loading. The mean steady-state skin fluxes were in the following order: silicone-2920 > PIB > silicone-2675 > acrylate. On the other hand,

however, no systematic trends in the lag times were observed. The addition of silicone oil to silicone-2920 adhesive to improve the tackiness of the patch had little or no effect on the skin flux of fentanyl. The silicone-2920 and PIB monolithic matrix patches provided several times higher skin flux of fentanyl as compared to other adhesives studied. It is interesting that, even though the acrylate adhesive and to some extent the silicone-3675 adhesive exhibited a relatively higher release rate in water, the skin fluxes from these monolithic matrices were considerably lower than those from the other two matrix devices.

Figure 5 shows the interval skin flux of fentanyl as a function of drug loading in the PIB. The steady-state skin flux was attained within 5 h after application of the matrix patch, and the flux was maintained for 3 days. The time to reach steady-state skin flux (T_{ss}) was not influenced by the drug loading in the PIB adhesive. Therefore, it could be safely assumed that the diffusivity of fentanyl in the skin was not significantly influenced by the drug loading in the PIB adhesive. The most striking feature of this study was that the skin flux increased as the drug loading in the PIB adhesive increased from 1% to 4%. The skin flux, however, did not increase significantly beyond 4% loading, which was likely because of the attainment of drug saturation in the PIB adhesive as discussed in the release kinetic studies.

Figure 6 shows a double plot of skin flux and release rate versus fentanyl loading in the PIB adhesive. The release rate increased as the drug loading was increased from 1% to 4%. A corresponding increase in skin flux with an increasing drug release rate was observed as the drug loading was increased from 1% to 4%. From Figure 6, it is quite clear that the skin flux of fentanyl did not increase significantly beyond 4% drug loading because of attainment of maximum thermodynamic activity of fentanyl in the PIB adhesive. These results suggested that the drug loading in the PIB adhesive had reached maximum thermodynamic activity and that the drug transport through cadaver skin beyond 4% loading was limited by dissolution of an excess of dispersed drug crystals in the PIB matrix.

Conclusions

In summary, the diffusion coefficient of fentanyl in silicone-2920 adhesive was the highest among the four pressure-sensitive adhesives examined. The silicone-2920 with 2% drug loading provided the highest skin flux. Because of low drug solubility, a high diffusion coefficient, and a low $K_{p,w}$, the silicone-2920 adhesive appears to be a very promising adhesive candidate for designing a transdermal device with minimum drug loading to sustain the delivery of fentanyl at a desired rate to induce analgesia in humans for the relief of acute and chronic pain. It was clearly demonstrated that the skin flux of fentanyl increased linearly as the drug loading in the PIB adhesive increased from 1% to 4%, and reached a plateau beyond 4% drug loading.

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